and are uncertain about why community members are dying from what appear to the survivors to be unusual causes. Although Hrudey may feel this concern is misplaced or unfounded, that opinion does not reflect the feelings of those who live in Fort Chipewyan. The Alberta government's assertion that more extensive health studies are warranted (Chen 2009) and stated intention to actively pursue such studies (Weinhold 2011) suggest adverse health effects are at least plausible.

Bob Weinhold
Freelance Science Journalist
Colorado City, Colorado

Susan M. Booker
News Editor, *EHP*
Research Triangle Park, North Carolina
E-mail: booker@niehs.nih.gov

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Neurotoxicity of PBDEs on the Developing Nervous System

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Dingemans et al. (2011) published a review article on polybrominated diphenyl ethers (PBDEs) and the developing nervous system. However, the authors summarized but failed to critically evaluate the articles cited in their review. They also did not discuss or cite literature that contradicted the studies on which they based their conclusions. For example, the U.S. Environmental Protection Agency (EPA) cosponsored an expert panel on neurodevelopmental end points, which concluded that an experimental design used in nine of the studies cited by Dingemans et al. (2011) failed to control for litter effects (Holson et al. 2008).

Although some investigators have set forth the argument that direct dosing of pups precludes the need to control for litter effects, a U.S. EPA cosponsored expert panel (Moser et al. 2005) evaluated this issue and concluded otherwise.

Regardless of whether Dingemans et al. (2011) view the studies by Holson et al. (2008) and Moser et al. (2005) as credible, the authors should have discussed them to some degree. It is understandable that because of space limitations not all studies can be included in a review. However, it was unacceptable to exclude studies that carry the weight of U.S. EPA cosponsored expert panels or other reviews that critically evaluated many of the studies cited by Dingemans et al. (2011) (e.g., Goodman 2009; Hardy et al. 2009; Williams and DeSesso 2010) and came to opposite conclusions.

Although the article by Dingemans et al. (2011) was peer-reviewed, it presents information in a selective, noncritical manner, which is best reserved for public relation pieces communicated in the non–peer-reviewed media.

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Marek Banasik
Dominika Suchecka
Institute of Public Health and
Environmental Protection
Warsaw, Poland
E-mail: iphep.banasik@gmail.com

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Neurotoxicity of PBDEs: Dingemans et al. Respond

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Banasik and Suchecka express their discontent with our recent review on the (in-)direct neurotoxic effects of parent and hydroxylated (OH-) polybrominated diphenyl ethers (PBDEs) on the (developing) nervous system (Dingemans et al. 2011). Their main discontent appears to be once more related to the experimental design in a number of cited behavioral studies. However, our aim was to identify and review the mechanisms underlying the observed adverse (behavioral) effects, not to evaluate the experimental design of behavioral studies within a regulatory setting. Nonetheless, approximately 10% of our review was dedicated to describing a number of behavioral studies [12 different studies from seven different research groups, including a 2008 EPA study (Gee and Moser 2008)] that all indicated the occurrence of neurobehavioral effects following developmental exposure to PBDEs. We used this information to create a starting point for the main part of our review of direct and indirect cellular and molecular mechanisms. For readability and space limitations, we were not able to include all studies, concerns, or critiques that have ever been raised. The absence of a citation to a particular study does not mean that we regard it as less credible.

The view that (developmental) exposure to PBDEs induces adverse neurotoxic effects is widely supported by numerous *in vivo*, *ex vivo*, and *in vitro* studies reporting both structural and functional effects (Dingemans et al. 2011). For some time, a lively discussion has been taking place within the scientific community on the experimental design for behavioral developmental neurotoxicity studies for regulatory purposes, in particular considering the statistical unit (Alcock et al. 2011). In short, there is disagreement about whether direct dosing of pups precludes the need to control for litter effects (e.g., Eriksson 2008; Hardy and Stedeford 2008). However, we did not address this topic in our paper because we consider the potential occurrence of a litter effect to be irrelevant for the reviewed cellular and molecular *in vitro* studies, which all indicate that exposure to PBDEs induces neurotoxic effects.

Critical remarks can be found throughout our review (Dingemans et al. 2011), but they are related to cellular and molecular findings, data gaps, or aspects that warrant further investigation. Our main conclusions are related to the specific (developmental) neurotoxic hazard of OH-PBDEs compared with that of their parent congeners via direct neurotoxicity and thyroid disruption. We also pointed out the need to further investigate the impact of active metabolites, concentrations of PBDEs and metabolites in the (developing) brain, and the potentially increased neurotoxic hazard following exposure to mixtures of different environmental contaminants.

Nonetheless, Banasik and Suchecka raise an important issue: the existence of differences in experimental designs for *in vivo* investigation of (developmental) neurotoxicity. Differences exist in the selection of investigated end points and also in methodologies for the investigation of a specific end point, as reviewed for effects on motor activity by brominated flame retardants (Williams and DeSesso 2010). These differences in experi-

mental design may underlie observed differences in sensitivity to detect neurotoxicity, possibly because of differences in biokinetics and exposure during sensitive windows of development. Fortunately, much effort is taking place in the scientific community to optimize experimental designs at different levels of biological complexity, including (developmental) neurobehavioral studies. Although a critical review on the impact of different experimental designs for *in vivo* (developmental) neurotoxicity studies would be very useful, it was beyond the scope of our review (Dingemans et al. 2011).

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Milou M.L. Dingemans
Martin van den Berg
Remco H.S. Westerink
Institute for Risk Assessment Sciences
Utrecht University
Utrecht, the Netherlands
E-mail: m.dingemans@uu.nl

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Three Criteria for Ecological Fallacy

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In a large cohort study published in *Environmental Health Perspectives*, Brenner et al. (2011) confirmed previous results on I-131 exposure and thyroid cancer among a Ukranian population. According to the authors, one motivation to study this association was based on evidence from ecological studies (Jacob et al. 1999) with two methodological limitations: use of grouped doses and poor control of confounding. With these new findings, evidence from ecological, case–control, and cohort studies are consistent; thus, an interesting question is whether there was an ecological fallacy.

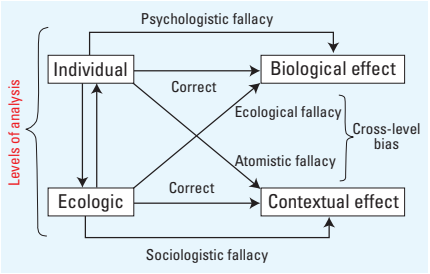

Figure 1. Levels of analysis in epidemiologic studies and potential fallacies during causal inference.

Although ecological studies are important to epidemiology (especially in environmental and social epidemiology), public health practitioners seem afraid of ecological studies. It is a common practice to assume the presence of ecological fallacy (Robinson 1950) and low-level validity when analyzing an ecological study. Most epidemiologists prefer an exclusive individualistic approach, although the importance of a multilevel causal approach is widely recognized (Diez-Roux 2002). In this sense, some authors suggest that it is as important to recognize the presence of ecological fallacy as to recognize psychologistic or individualistic fallacy (Subramanian et al. 2009) (Figure 1).

Thus, it is necessary to have clear guidelines on when there is or not an ecological fallacy. In this sense, I propose three criteria for the identification of ecological fallacy; all three of these should be present to confirm its existence:

- Results must be obtained with ecological (population) data.
- Data must be inferred to individuals. One use of ecological studies is to explore individual-level association when individual data are not available. When the focus of the study was contextual or based on population effects and there is no inference to individuals, ecological fallacy is not possible. When only the first two criteria are present—which is insufficient to affirm ecological fallacy—it is appropriate to acknowledge that there is a possible relationship and that further study is required.
- Results obtained with individual data are contradictory.

Only when empirical data are available is it possible to confirm that an ecological fallacy is present.

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Alvaro J. Idrovo
Center for Health Systems Research
National Institute of Public Health
Cuernavaca, Morelos, Mexico
E-mail: javier.idrovo@insp.mx

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Carbon Black

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In "Research Recommendations for Selected IARC-Classified Agents," Ward et al. (2010) identified research gaps for 20 occupational agents "based on evidence of widespread human exposures and potential carcinogenicity in animals or humans." (Ward et al. 2010) For carbon black, the authors suggested that

> Research needs include updating epidemiology cohorts with data on work histories and exposures in relation to particle size and surface area, and recruitment of additional carbon black facilities. The relationship between occupational exposure to carbon black and validated biomarkers of oxidative stress should be examined and exposure–response relationships in humans and rodents quantified, including the role of particle size.

Ward et al. (2010) referred to a study of British carbon black workers in which carbon black was suggested as a possible "late stage carcinogen" (Sorahan and Harrington 2007). In that study, Sorahan and Harrington (2007) called for similar analyses of other carbon black cohorts (i.e., evaluating the possibility of carbon black acting as a late stage carcinogen via the concept of "lugging," which considers only recent exposures and not historical exposures). In response to suggestions made by Sorahan and Harrington, we conducted such analyses on a large German carbon black cohort (Morfeld and McCunney 2007, 2009). We were unable to reproduce the results of the British analysis, despite the elevation noted in lung cancer among German cohort workers, thus providing no support for the late stage-lugging hypothesis. Results of a detailed analysis of the German cohort using Bayesian methodology showed smoking and exposure to occupational carcinogens prior to work at the carbon black plant as confounders probably responsible for the lung cancer excess (Morfeld and McCunney 2010).

Ward et al. (2010) called for enhanced exposure–response assessments in humans. Currently, a dose–response exposure analysis is under way on the U.S. carbon black cohort (> 5,000 production workers). An earlier evaluation of this cohort showed no increase in any type of cancer (Dell et al. 2006).